The experience-dependent increase in deep sleep activity is reduced in children with attention-deficit/hyperactivity disorder

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The experience-dependent increase in deep sleep activity is reduced in children with attention-deficit/hyperactivity disorder.

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Abstract

Objective/Background

Learning of a visuomotor adaptation task during wakefulness leads to a local increase in slow-wave activity (SWA, EEG power between 1 and 4.5 Hz) during subsequent deep sleep. Here, we examined this relationship between learning and SWA in children with attention-deficit/hyperactivity disorder (ADHD).

Patients/Methods

Participants were 15 children with ADHD (9.7 – 14.8 y, one female) and 15 age-matched healthy controls (9.6 – 15.7 y, three female). After the completion of a visuomotor adaptation task in the evening, participants underwent an all-night high-density (HD, 128 electrodes) sleep-EEG measurement.

Results

Healthy control children showed the expected right-parietal increase in sleep SWA after visuomotor learning. Despite no difference in visuomotor learning, the local up-regulation during sleep was significantly reduced in ADHD patients compared to healthy controls.

Conclusions

Our results indicate that the local, experience-dependent regulation of SWA is different in ADHD patients. Because the customarily observed heightened regulation in children was related to sensitive period maturation, ADHD patients may lack certain sensitive periods or show a developmental delay.

Keywords

ADHD; high-density EEG; slow-wave activity; development; sensitive period maturation; local sleep

1. Introduction

The need for sleep is best reflected in slow-wave activity (SWA, EEG power between 1 and 4.5 Hz) during deep sleep (Achermann and Borbély, 2017). There is compelling evidence indicating that the build-up of sleep need is dependent on daytime experience (Diekelmann and Born, 2010; Tononi and Cirelli, 2019). For example, SWA is up-regulated over the right-parietal cortex after learning a visuomotor adaptation task (Huber et al., 2004; Määttä et al., 2010), suggesting that sleep need (i.e., SWA) increases as a function of experience-dependent plasticity. This change in SWA supposedly reflects plastic changes underlying the consolidation of the learned task in the brain area crucial for visuomotor integration (Ghilardi et al., 2000). Note that deep sleep SWA is considerably higher in children than in adults (Campbell and Feinberg, 2009; Kurth et al., 2010). Correspondingly, during development, when the maturating brain shows the highest plasticity, the experience-dependent increase in SWA is most pronounced (Wilhelm et al., 2014). Together, these findings indicate that local experience-dependent regulation of SWA reflects sensitive periods during maturation.

Children with attention-deficit/hyperactivity disorder (ADHD) show an anterior-posterior imbalance as well as a global reduction in SWA compared to healthy age-matched children (Ringli et al., 2013; Furrer et al., submitted). Thus, we tested whether the local increase in SWA following a visuomotor adaptation task is less pronounced in ADHD compared to healthy participants, to provide insights into the role of deep sleep in ADHD.

2. Methods

1.1 Participants

To test this hypothesis, 15 children with ADHD (9.7 – 14.8 y, mean: 12.4 y, 1 female, 1 left-handed) meeting the DSM-IV criteria were recruited from the Department for Child and Adolescent Psychiatry of the University of Zurich (data of 9 subjects published previously in Ringli et al., (2013)). Eight ADHD patients received no psychostimulant medication during the time of their participation in the study. Seven of these children have never received psychostimulants, and one participant was treated with methylphenidate until two years before the start of the study. The remaining seven ADHD patients were receiving methylphenidate (Concerta, Ritalin) on a regular basis (mean: 45.29 mg/day, range: 15 – 80 mg/day). One of these patients refrained from the intake of medication on the day of the sleep assessment.

15 sex- and age-matched healthy controls (9.6 – 15.7 y, mean: 12.3 y, three female, all right-handed) were included from a study published previously by (Wilhelm et al., 2014). Healthy controls were never diagnosed with a psychiatric disorder and did not take any medication during the period of assessments.

Six months prior to the study, no participant traveled across more than one time zone. During the seven days before the sleep assessment, a regular sleep-wake rhythm was maintained as verified with wrist accelerometry (Actiwatch Plus, AW4, Cambridge Neurotechnology) and sleep diaries. Written informed consent was obtained from a parent, the study was approved by the local ethics committee and performed according to the Declaration of Helsinki.

1.2 Procedures

All participants underwent an all-night high spatial resolution (high-density, HD) sleep-EEG measurement (128 electrodes) in the sleep laboratory of the University Children's Hospital Zurich (preprocessing of EEG-data in Supplementary Methods). Healthy control participants underwent two night recordings (rotation and baseline condition) separated by at least one week with the order of conditions balanced across subjects. In the evening of each condition, they performed a visuomotor adaptation task in which they moved a cursor from a central starting point to one of four target points in a pseudorandomized order. In the rotation condition, the visual feedback of the target points was rotated at a fixed angle. The learning session consisted of four rotation-blocks (15°, 30°, 45°, and 60°), each comprising three trials with the same rotation angle. In each of the trials, subjects had to execute 44 movements. After each trial, subjects received visual feedback about their performance. Learning was parametrized by measuring the directional error at peak velocity (Fig. 1a). In the baseline condition, participants performed the same number of movements without any rotation. A detailed description of the task can be found in (Wilhelm et al., 2014). As a major limitation of the study, ADHD patients only participated in the rotation condition.

1.3 Data analysis

SWA was averaged over the first hour of artifact-free NREM sleep because this yields a reliable estimate of deep sleep brain activity (Lustenberger et al., 2017). As in previous investigations addressing local sleep EEG topography (Ringli et al., 2013; Wilhelm et al., 2014), SWA was normalized by dividing the value of each electrode by the mean across all electrodes. To investigate the learning-induced increase in right-parietal SWA, the brain area crucial for visuomotor integration

(Ghilardi et al., 2000), during the rotation condition independent of a baseline recording, electrode-wise one-sided paired t-tests were applied to compare the right- with the left brain hemisphere. To disentangle possible naturally existing hemispheric asymmetries in the level of SWA, we performed this analysis for the baseline condition.

To account for multiple testing, we defined a cluster of electrodes as minimally six significant neighboring electrodes, because when calculating statistical tests across electrodes (one-sided, significance level of 5 %), five electrodes will become significant by chance. A similar approach was used previously (Wilhelm et al., 2014).

3. Results

We first analyzed the learning efficiency during the task before sleep and found that ADHD patients showed no differences in the learning curve compared to healthy controls. Furthermore, neither the rhythmicity nor straightness of the executed movements differed between the groups, indicating that the cognitive effort to complete this task was similar in ADHD and control participants (Fig. 1b, see also Supplementary Table S1, Supplementary Methods for more information). Thus, we would expect similar experience-dependent plastic changes in both groups before sleep.

Next, we confirmed previous findings of locally increased parietal SWA in the rotation- compared to the baseline condition (Wilhelm et al., 2014) during the first hour of artifact-free NREM sleep in the control group (Fig. 1c, top). To overcome the study design limitation in ADHD patients, we used the left hemisphere of the rotation condition as a "baseline," which is a way to estimate the experience-dependent SWA change without a baseline recording (Poryazova et al., 2015). When performing this comparison in healthy controls, we found a cluster of twelve electrodes with significantly increased SWA over the right cortex (Fig. 1c, bottom left). To exclude pre-existing asymmetries, we performed the same comparison for the baseline condition (Fig. 1c, bottom right). Visual inspection of this comparison suggests that the SWA increase over the parietal cortex is exclusive to the rotation condition. The positive correlation between the right-parietal SWA increase after the rotation compared to baseline and the local difference in SWA when comparing the right to the left hemisphere in the rotation condition only ($r = 0.78$, $p = 0.0006$) supports our approach.

Thus, we used this “right-left hemisphere” approach to test if ADHD patients differ from healthy controls in terms of the experience-dependent local SWA increase. Electrode-wise 2 x 2 ANOVA with the factor group and the within-group factor brain hemisphere revealed no significant main effect of group or brain hemisphere, but a significant interaction between the two in a cluster of six parietal electrodes (F(1,28) = 10.68, p = 0.0029), indicating that ADHD patients differ from healthy controls in the experience-dependent increase of local SWA (Fig. 1d). Indeed, a direct comparison showed that the local change in SWA is reduced in ADHD patients compared to healthy controls (Fig. 1e). The small sample size limited the analyses of the effects of medication, gender, and handedness (see Supplementary Results). Sleep efficiency and architecture did not differ between groups, while total time in bed was longer in ADHD than control participants (Supplementary Table S2). Because only the first hour of NREM sleep was analyzed, this should not have influenced the results. Potential first night effects could not be assessed in the ADHD group because ADHD patients spent only one night in the sleep laboratory. In the control group, however, first and second nights did not differ in terms of sleep architecture nor SWA topography (data are not shown).

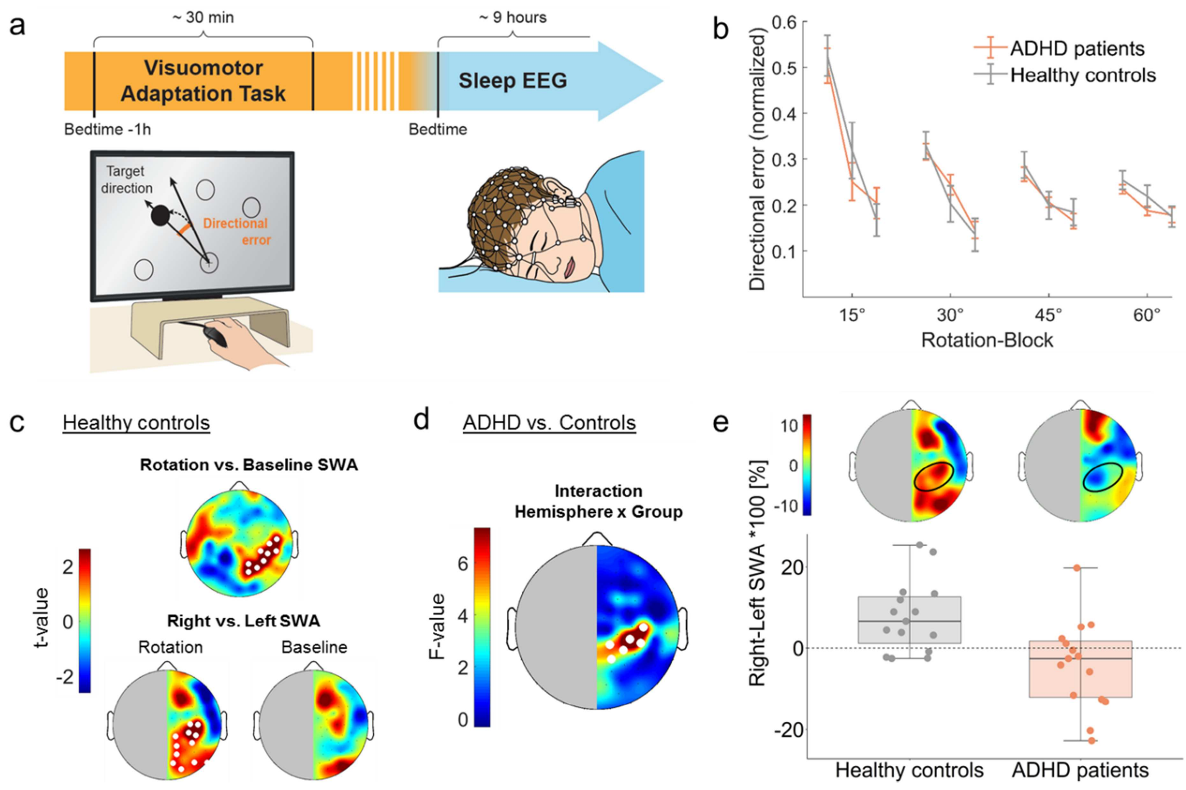

Figure 1. (a) Experimental design. Subjects performed a visuomotor adaptation task in the evening before an all-night sleep HD-EEG recording. Directional error represents the angle between the line from the initial hand position to the position of the target and the line to the position of the hand at the peak outward velocity. (b) Learning curves with normalized directional error (divided by rotation angle). ADHD patients (n = 15) and healthy controls (n = 15) improved across trials and rotation blocks (p <

0.0001 for main effect of trial and block; p = 0.8078 for main effect of group). (c) Top: T-values resulting from electrode-wise Student's one-tailed paired t-tests comparing SWA (first hour of artifact-free NREM sleep) of the baseline session with SWA of the rotation session in healthy controls. Bottom: T-values comparing SWA of the right hemisphere with SWA of the left hemisphere in healthy controls for the rotation and the baseline sessions. White dots represent electrodes with a significant SWA increase ($p < 0.05$). (d) Electrode-wise interaction between brain hemisphere and group. F-values are represented on the scalp map with significant electrodes in white. (e) Topographical distribution of the difference between right and left SWA and boxplots displaying the mean difference over the cluster of six electrodes showing a significant interaction.

4. Discussion

Learning a task during wakefulness causes a build-up of sleep need, which is best reflected in the initial increase of SWA (e.g., the first hour of sleep) during subsequent sleep. Even though ADHD patients learned a visuomotor adaptation task equally well as their normally developing peers, we observed no corresponding build-up of SWA. Hence, the general reduction in SWA found in ADHD patients (Furrer et al., submitted) could be the result of a reduced experience-dependent build-up of sleep need. As the heightened experience-dependent regulation of SWA in children was related to sensitive period maturation (Wilhelm et al., 2014), ADHD patients may lack certain sensitive periods or simply show a developmental delay.

Our results may also relate to behavioral consequences, since the up-regulation of SWA after learning is necessary for sleep-dependent performance gains (Huber et al., 2004; Landsness et al., 2009). Notably, the memory consolidating effects of sleep were not found in ADHD patients (Prehn-Kristensen et al., 2013, 2011). Moreover, boosting SWA by transcranial oscillatory direct current stimulation, presumably bringing it to normal levels, improved declarative memory consolidation in children with ADHD (Prehn-Kristensen et al., 2014). Unfortunately, we did not assess task performance after sleep in our participants and therefore, cannot draw any direct conclusions related to sleep-dependent performance.

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3. Declaration of interest

None.

4. Supplementary Material

Supplementary Table S1

Supplementary Table S2

Supplementary Results

Supplementary Methods

- EEG slow-wave activity (SWA) during sleep reflects experience-dependent plasticity.
- Visuomotor learning before sleep was normal in children with ADHD.
- The experience-dependent SWA increase during subsequent sleep was reduced in ADHD.